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Protocol 5

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13. ABSTRACT (Maximum 200 words) In a substantial percentage of women, current non-invasive tests, lack both sensitivity and specificity for determining the presence of coronary artery disease and prognosis. Myocardial perfusion imaging with radio-pharmaceuticals significantly increases both sensitivity and specificity of exercise testing studies. However, attenuation artifacts in woman continue to cause false positive results. Until recently, attenuation artifacts (from breast, diaphragm, bone and soft tissue), the greatest cause of false positive studies, could not be corrected. A very Promising and significant recent development is the STEP protocol, whereby attenuation can be corrected by means of application of an attenuation map to radionuclide perfusion data. This may allow for a) unification of separate gender data bases, b) increase in specificity by eliminating false positive studies which result from attenuation artifacts, or c) allow for inclusion of large breasted women in existing data bases. The specific issues of the quantitative effect of breast and diaphragmatic attenuation on perfusion imaging, although very important, have not been adequately investigated because there has been no easy way of correcting or measuring attenuation until now.				
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FOREWORD

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I. Introduction and background:

The accuracy and adequacy of the diagnosis of coronary artery disease (CAD) in women has been the subject of much controversy. In a substantial percentage of women, current non-invasive tests, such as ECG-monitored graded exercise tests and echocardiography, lack both sensitivity and specificity for determining the presence of coronary artery disease and prognosis. Myocardial perfusion imaging with radiopharmaceuticals, most recently with ^{99m}Tc -Sestamibi, significantly increases both sensitivity and specificity of exercise testing studies. These radiopharmaceutical studies are routinely used for diagnostic and prognostic testing. However, attenuation artifacts in women continue to cause false positive results, thereby increasing medical costs and risk, because these women often require coronary angiography for definitive diagnosis, an expensive and not risk-free procedure.

Until recently, attenuation artifacts (from breast, diaphragm, bone and soft tissue), the greatest cause of false positive studies, could not be corrected. Consequently, a significant proportion of women could not be adequately evaluated non-invasively, and separate data bases based on gender have had to be generated. Since women are under-represented in these data bases, and large breasted women (c-cup and larger), and overweight women are excluded from them, the data bases suffer from lack of statistical power in the female population. A very promising and significant recent development is the STEP protocol, whereby attenuation can be corrected by means of application of an attenuation map to radionuclide perfusion data. This may allow for a) unification of separate gender data bases, b) increase in specificity by eliminating false positive studies which result from attenuation artifacts, or c) allow for inclusion of large breasted women in existing data bases. The military population is an ideal one for this study, since the proportion of normal women inconclusively diagnosed by non-invasive means is higher than that seen by civilian cardiologists, who generally see an older and male biased population. The specific issues of the quantitative effect of breast and diaphragmatic attenuation on perfusion imaging, although very important, have not been adequately investigated because there has been no easy way of correcting or measuring attenuation until now.

In order to accurately diagnose myocardial perfusion defects in women, normal data bases have been established. However, these data bases did not take into account large breasted nor overweight women. By using corrective algorithms generated by an attenuation map, the effects of attenuation artifacts on the interpretation of myocardial perfusion studies will be evaluated - both quantitatively and semiquantitatively. If there is a significant statistical difference between the corrected and uncorrected images, attenuation correction may become the standard for large breasted or overweight women in myocardial perfusion imaging.

II. Objectives to be Met:

To quantitatively evaluate the distribution, severity, extent, and prevalence of breast, diaphragmatic and soft tissue attenuation artifacts during myocardial perfusion imaging using 99mTc-Sestamibi in women without coronary artery disease. To the present date, no report has been published in quantitating distribution, severity, extent, and prevalence of breast and diaphragmatic attenuation artifacts in women without coronary artery disease using 99mTc-Sestamibi for cardiac SPECT. Overall, we propose a pilot study for evaluating the breast and diaphragmatic attenuations in women with 1) bra size of C or greater, 2) 10% over upper limits of lean weight, and 3) less than 5% likelihood of having coronary artery disease (11). We will specifically use 99mTc-Sestamibi-153Gd pair for STEP in SPECT in correcting for tissue attenuation artifacts (12). Quantitative corrected and uncorrected images as well as visual score grading system of 0 to 4 will be compared with the already established data base for 99mTc-Sestamibi imaging and with a population of women at this institution similar to the CEQual data base population (9). The effect on the variables of breast size and body habitus on apparent perfusion will be analyzed to determine if attenuation correction significantly changes the normal limits in the CEQual data base.

It is estimated that a total of 75 female patients will be necessary for completion of this pilot study. These patients will be referred from the Cardiology and Internal Medicine Clinics at Fitzsimons Army Medical Center and other near by military facilities through physician referrals generated through a recruiting flyer, and a general information flyer for common area distribution.

III. Results:

The imaging table, and STEP specific hardware/software and treadmill equipment are due for repairs/upgrades in the month of August, 1995. Testing of cardio-fan collimators is complete with good results. Computer program to quantify CEQual data has been developed which will display mean and standard deviations for the three groups. Development of cardiac phantom in thorax cavity is complete, use of this phantom will help to analyze the camera/software system prior to live subject testing. Development of phantom and testing plans are also complete. Minor changes to the Volunteer Agreement Affidavit, Medical Office and general disbursement advertising are complete, pending IRC and HURRAD approval, expected August, 1995. The patient recruitment process will begin following testing/training of equipment and personnel.

Future Plans for Quarters Three, Four, Five and Six

1. Recruitment and testing.

a. Inclusion criteria: DEERS-eligible females over the age of 30 and less than age 55 with a low likelihood of coronary artery disease. They will be defined as being normal by having a <5%

likelihood of CAD, based on sequential Bayesian analysis of age, sex, symptom classification and the results of exercise electrocardiography. These criteria will be identical to those used in the generation of the current CEQual female data base, except for those women of large body habitus (under represented in the CEQual data base [personal communication from Dr. K. Van Train CEQual Coordinator] and large breasted women (c cup or larger) excluded from the CEQual data base. This method of defining normals allows selection of a normal population closer in age to the CAD population without subjecting normal patients to potentially dangerous cardiac catheterization.

b. Exclusion criteria will include women who are pregnant or declare themselves as pregnant. If a patient is unsure, a serum pregnancy test will be performed. In addition, patients with history of congenital or valvular heart disease, cardiomyopathy, or left bundle branch block will be excluded.

c. Study patients will be asked to discontinue beta-blocking medication for 24 to 48 hours prior to study and long-acting nitrates for 4 hours before the study. Rest images will be acquired one hour after injection to allow for clearance from the hepatobiliary system. To promote tracer clearance, patient will drink 8 ounces of whole milk or ingest a light fatty meal 15 minutes before imaging.

d. An interval of 3 to 4 hours will be employed between the rest and stress study to allow radioactivity from the rest dose to decay 29% to 37% by the time of stress imaging. Exercise will then be performed using a standard graded treadmill test (Bruce protocol). Exercise will be symptom-limited (moderately severe anginal pain, severe dyspnea, or severe fatigue), unless one of the following criteria for termination of exercise develops: 4 mm ST segment depression/elevation, malignant dysrhythmia, exercise hypotension (>10 mm Hg drop between exercise stages). If the patient has LVH or is taking digoxin, the ST segment response will not constitute reason for termination. Exercise will continue for at least one minute after injection, and imaging begun 30 minutes after exercise.

e. Acquisition Protocol: Protocol SPECT images will be acquired in the supine position, arms raised above the head, on the Picker Prism 3000 3 headed gamma camera using both high resolution parallel hole collimators and high resolution fan beam (cardio fan) collimators at both stress and rest. The order of use of parallel hole collimators will be randomly changed among patients, followed by the fan beam collimators at both stress and rest. When the fan beam collimators are being used, a transmission line source (Gadolinium-153) will be positioned at the focal point of one of the heads of the gamma camera. The following protocols will be used.

f. Rest and stress parallel hole collimator images on modified CEQual protocol: Using a step-and-shoot protocol, magnification 1.3, every 3° for 180° , beginning at the 45° LPO to the 45° RAO positions in relation to the patient, 60 images in a 64×64 pixel matrix will be acquired. Images will be acquired for 25 seconds per projection at rest and 20 seconds per projection at stress using a 20% energy window centered over the 140 keV photopeak. Study time will be 19 and 16 minutes respectively for rest and stress.

g. Rest and stress fan beam collimator attenuation correction protocol: Using a continuous acquisition, magnification 1.0, every 3 degrees for 360 degrees, 120 images will be obtained in a 64×64 pixel matrix. Images will be acquired using a 20% window centered on both the 140 keV and 100 keV photopeak for all 3 heads. Imaging time will be 10 seconds per projection at rest, 8.5 seconds per projection at stress, for a total of 19 minutes for rest images and 16 minutes for stress images, or to a time empirically determined to give approximately equal total counting statistics for each image set between fan beam and parallel hole collimators, not to exceed 25 minutes total imaging time for rest and 20 minutes for stress images.

2. Data Processing/Reconstruction:

a. Parallel hole collimator: The Cedar-Sinai CEQual processing protocol will be adhered to. Prefiltering of raw data is done using a 2 dimensional Butterworth filter, with an order of 5, cut-off of .25 Nyquist for rest studies and an order of 2.5, critical frequency of .332 for stress studies. Transaxial tomograms are reconstructed using a ramp filtered back projection to a pixel thickness of 6.4 mm.

b. Fan beam collimator data reconstruction: Images from identical image angles from all 3 heads in the 140 keV window will be summed to yield 120 total projections. Data from the 100 keV window in the 2 heads not imaging the Gadolinium-153 flood source will be used to correct the data from the head opposite the Gadolinium-153 flood source for Technetium-99m down scatter into the Gd-153, 100 keV window and an attenuation map derived using an iterative maximum likelihood algorithm. After down scatter correction, the emission data in the 140 keV window will be simultaneously reconstructed and attenuation corrected using the already derived attenuation map using a 20 iteration maximum likelihood reconstruction algorithm. The resulting transaxial images will then be zoomed with the appropriate conversion factor to achieve a pixel size of 6.4 mm. These images will then be filtered with a 3 dimensional Fourier filter using an order 5, critical frequency .25 Nyquist for the rest studies and an order of 2.5 critical frequency .332 Nyquist, for the stress studies.

(parallel hole: rest, stress and fan beam: rest, stress, respectively) will subsequently be reformatted and displayed in an identical manner. All the above data sets will be reformatted such that 3 additional data sets for each of the above data sets are obtained: 1 slice set perpendicular to the long axis of the heart (short axis slices) and 2 sets orthogonal to each other but parallel to the long axis of the heart (horizontal and vertical long axis slices). Adjacent slices in each data set will then be added in staggered summation to produce a new set of 3 orthogonal tomograms each representing a 12.8 mm slice thickness with equal spatial resolution in all directions. The highest count pixel in the heart will be interrogated and the entire data set (short, vertical long and horizontal long axis images) truncated to that value.

d. CEQual Program: For each of 4 studies performed on each volunteer, an automatic image processing program approved in a Beta-test version at FAMC last year will be used. Briefly, all the above generated short axis images are manipulated such that "bull's eye" apical spherical slices and mid and basal ventricular slices are generated (Appendix D, Fig 1) and divided into up to 12 profiles with a total of 480 points. For analysis purposes the above profiles are normalized. This is done by consolidating the 480 points in an already determined normal data base apical and cylindrical slices into 10 perfusion territories and generating a mean count for each territory (Appendix F, Fig 2). A scale factor is determined by comparing the most normal territory in the patient's heart with the corresponding territory in the normal data base. All 480 points in the patient's heart are multiplied by this scale factor and a severity assessment for each point defined by equation 1 (Appendix F, Fig 7) is determined. In this equation, Spt represents the degree of severity in terms of number of standard deviations by which one of the 480 patient profile points is above or below the mean normal value. Threshold abnormal values have already been determined empirically using ROC analysis on the normal data base to be 10% abnormal pixels in a myocardial territory. Optimum standard deviation thresholds for all 480 individual points were assigned after interpolation of abnormal thresholds determined for each territory (Appendix F, Fig 6).

3. Visual defect determination: For each of the 4 studies performed on each volunteer, short axis, horizontal and vertical long axis images will be displayed in the usual manner on the computer monitor without windowing or leveling using a linear grey scale. A visual segment overlay will be used (Appendix F, Fig 3): Expert visual evaluation of these segments using the following criteria will be performed:

- 0 - no defect
- 1 - mild defect not thought to be true perfusion defect
- 2 - moderate defect thought to be a true perfusion defect
- 3 - severe defect - only mild activity remaining in the segment
- 4 - no activity

Statistical analysis: The volunteer studies will be divided into 3 groups:

Group 1 - 25 patients ≤ 10 percent over the maximum allowable weight as determined by Metropolitan Height-Weight Tables and bra cup size $\leq B$.

Group 2 - 25 patients bra size $\geq C$ cup size.

Group 3 - 25 patients $\geq 10\%$ upper limit of lean body weight (by Metropolitan Height-Weight Tables).

Visual analysis: Group 1 rest and stress images from the parallel hole collimator studies will be viewed unblinded in joint conference by 3 expert observers to establish a common normal reading by visual assessment. An additional 25 patients having Sestamibi studies with known coronary disease will be viewed jointly and visual criteria 0 through 4 agreed upon. All 3 group's images (4 sets per volunteer) will be evaluated in a blinded fashion by a consensus reading of 3 expert observers using the visual criteria above and scores for each segment recorded. During this evaluation, images from the 25 patients with coronary disease will be randomly mixed with the 3 groups, but will not be evaluated statistically, to prevent interpretation bias which may occur from knowing all patients are "normal".

Group 2 and 3 of volunteers will be paired with Group 1. Within each pairing the abnormality rate (normal defined as 0-1, abnormal 2-4) for the group (total abnormal segments within the group divided by the total possible segments within the group) will be determined for the following combinations analyzed for statistical significance at the $p=.05$ level:

Parallel hole stress - both groups

Fan beam stress first group - parallel stress 2nd group

Fan beam stress - both groups

Parallel stress first group - fan beam stress 2nd group

If a significant difference is found, a clustering analysis using a chi square analysis will be performed to determine which segments are responsible for the significant difference.

Within each group the abnormality rate for each image acquisition (defined as the average number of segments which are abnormal per volunteer) will be determined for each volunteer's 4 image sets. The significance of differences in this rate (pairing the 4 combinations of the 4 tests within each volunteer) will be determined at the $p < .05$ level using repeated measures analysis of variance followed by Tukie-Kramer multiple comparisons test. The strength of clustering of abnormalities within each image set will be evaluated by a chi square analysis of expected abnormality distribution within walls.

4. Quantitative Analysis:

a. Each group will be compared to the normal data base and a percentage of pixels in the normal limit profiles at the $p < 0.05$ level will be determined. Analysis of each wall for evidence of clustering compared to the normal data base will be performed using the appropriate statistical test.

b. Normal distribution ratios for rest and stress, using the apical lateral segment as the standard will be generated and using the $\geq 10\%$ abnormal counts as the threshold of abnormality, for each of 4 walls (anterior, lateral, inferior, and septal walls), the standard deviation thresholds for each group and each of the 4 type acquisitions (rest and stress parallel and rest and stress fan beam) will be generated. The significance of the difference in these standard deviation thresholds at the $p = .05$ level from both the CEQual normal data base (i.e., pairing each of the 3 groups with the CEQual database) and Group 1 (i.e., pairing groups 2 and 3 with 1) will be determined.

c. In a manner similar to (a) and (b) above, the abnormality rate within each group for each of the 4 image acquisitions will be determined using the standard deviation threshold of both the CEQual normal data set and (if significantly different) the group 1 CEQual protocol data set. Using a sign test $p = .05$ level of significance, the significance of the differences in these rates, pairing the 4 combinations of the 4 tests within each volunteer, will be determined at the $p < .05$ level. Clustering will be analyzed by chi square analysis of expected abnormality distribution within the walls.

5. SPECIAL CONSIDERATIONS:

a. Departure from Protocol: There will be no departure from this protocol without approval of Chief, Clinical Investigation.

b. Adverse Reactions: Any severe reaction to the radiopharmaceutical will be immediately reported to the FDA, Chief of DCI, the Human Use Review and Regulatory Affairs Division (USAMRMC) and patient's primary care physician. This includes, but is not limited to angina, seizures and severe hypersensitivity (characterized by dyspnea, hypotension, bradycardia, asthenia and vomiting).

6. MODIFICATION OF PROTOCOL: The principal investigator will send a memorandum to the Chief, DCI requesting IRB approval of any modifications or change in investigators.

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